REMARKS

Claims 41, 42, 79, 81, 82 and 84 were pending in the subject application. By this amendment, Claims 81, 82 and 84 have been canceled without prejudice or disclaimer, Claim 41 has been amended, and new Claims 86-93 have been added. Applicant maintains that the amendments do not raise an issue of new matter. Support for the claim amendments can be found at least in the previous version of the claims. In regard to the feature introduced into Claim 41 ("a therapeutically effective amount of a selective serotonin re-uptake inhibitor"), therapeutically effective amounts of selective serotonin re-uptake inhibitors (SSRI), such as, for example, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, are well known in the art and can be found, for example, in the Physicians' Desk Reference, the manufacturer's product literature, the online Encyclopedia of Medical Disorders, and the online Wikipedia Encyclopedia. Entry of the amendment is respectfully requested.

Summary of October 22, 2009 Interview

Applicant thanks the Examiner for the courtesy of a personal interview that was held at the U.S. Patent Office on October 22, 2009 with the Examiner, applicant and applicant's attorneys. Applicant concurs with the Examiner's Interview Summary in which the Examiner indicated "Applicants' presented data showing the unexpected results with low dose (5-15 mg) pipamperone. Applicants' will consider amending the claims to advance prosecution." Data from the applicant are included in the accompanying Supplemental Information Disclosure Statement (SIDS) and discussed below.

Rejections under 35 U.S.C. §112

Claims 81, 82 and 84 are rejected as failing to comply with the written description requirement. Claims 81, 82 and 84 have herein above been cancelled, thereby rendering this rejection moot.

Rejections under 35 U.S.C. §103(a)

1. Claims 41, 42, 80, 81, 82, and 84 are rejected as being unpatentable over Wirz-Justice et al. (Alzheimer Disease and Associated Disorders 14(4): 212-215, 2000), Medicaments Psychotropics, and Dudley et al. (US 2004/0002482).

Applicant respectively traverses this rejection.

The present invention

Background: The claimed invention requires the administration of pipamperone in an unprecedented low dose of 5 to 15 mg. One of the main problems with contemporaneous psychoactive drugs is their side effects, which limit the usability of these drugs. For instance, the selective serotonin re-uptake inhibitors (SSRIs), which are generally considered to be the first-line antidepressants of choice, block the serotonin transporter responsible for pre-synaptic reuptake. Thus, the availability of synaptic serotonin is augmented, leading to a *stimulation* of various serotonin (5-HT) receptors. However, the simultaneous stimulation of the pre- and postsynaptic serotonin receptors results in several inhibitory effects. The enhanced availability of serotonin stimulates the 5-HT2A receptor which in turn has an inhibitory effect on 5-HT cell bodies via excitation of glutamatergic pathways and 5-HT1A receptor stimulation via specific intracellular biochemical pathways in 5-HT cell bodies. Hence, administration of SSRIs causes a negative feedback, which limits the antidepressant actions of these drugs.

Dose-effect of pipamperone: The inventor surprisingly found that the use of a *daily low dose of 5 - 15 mg* of pipamperone augments the effect of a SSRI in treating a disease or disorder with an underlying dysregulation of the emotional functionality. At the claimed daily low dose, the inventor surprisingly found that pipamperone has a specific, but double effect, *i.e.* a high selective D4 *and* 5-HT2A receptor antagonistic effect. Thus, serotonin, which has enhanced availability due to the action of the SSRI cannot bind to the serotonin 2A receptor. As a corollary, the efficacy of the SSRI is increased, but also the cognitive and behavioural problems induced by enhanced D4 stimulation in the meso-cortical cortex as a result of the augmented availability of dopamine via 5-HT2A antagonism is prevented. As such, pipamperone can exert its augmenting effect on the second, SSRI compound. This effect has not been described in the prior art, nor is there any hint towards such an effect. This daily low dose of pipamperone has *not* been used in the prior art.

Pipamperone as a sedative neurolepticum: In the prior art, pipamperone is used at higher doses acting as a *sedative neurolepticum* (see e.g. Squelart et al. (1977) as well as the manufacturer's instructions, both of record). As a corollary, the prior art teaches using the highest tolerable dose for treating psychoses. However, at these higher doses pipamperone has no therapeutic effect on the SSRI because an antagonistic activity towards the *D2* and *alpha-adrenergic* receptor takes place, which dominates the clinical effect. This is well-known in the art. This antagonistic activity happens in such a way that negative emerging symptoms like D2 antagonistic related signs such as emotional blunting and cognitive problems (the so-called "neuroleptic induced deficit syndrome") and alpha-adrenergic related signs such as dizziness, decreased blood pressure and drowsiness may counteract the symptoms of, but certainly not treat, and least of all, augment the effect of the SSRI in the treated mood or anxiety disorder.

The present invention does not involve a mere optimization of dosage by routine experimentation. Rather, it is well-known that pipamperone at the ubiquitously used (high) prior art doses indeed decreases the symptom of psychological anxiety (see e.g. "Dipiperon" of record). This effect of pipamperone results from a neuroleptic-sedative effect. Specifically, it is known that the high dose pipamperone results in D2 receptor-related dopaminergic and H1 receptor-related histaminergic antagonism, which is responsible for the neuroleptic-sedative effect. This antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day. Accordingly, there would be no incentive to decrease the amount of pipamperone administered, since this would lower the neuroleptic-sedative effect.

Indeed, as previously detailed, the prior art teaches away from using a low dose.

For instance, Dipiperon (of record) teaches away from this low dose range. For adults, Dipiperon on page 1 teaches an initial dose of 40 to 80 mg a day, and that if necessary the dose may be increased to a maximum of 360 mg per day. For children the initial dose is 20 mg per day, and the optimal therapeutic dose varies from 20 to 40 mg per day. There is no teaching or suggestion in the cited references to administer pipamperone at a lower dose than the recommended dose. To the contrary, the teaching is always to increase the dose.

In addition, it is noted that the World Health Organization lists a Defined Daily Dose (DDD) for pipamperone of 0.2 g (200 mg) (see download from WHO website in accompanying SIDS).

Applicant would like to address a point that the Examiner may not have fully appreciated. On page 11 of the June 10, 2009 Office Action, the Examiner indicated that applicant has shown an effect of 4 mg pipamperone and 10 mg citalopram in combination therapy. Applicant notes that the formula used in Table 2 of the application refers to

"2x(CIT(10mg) + PIP(4mg))/d" which amounts to 20 mg CIT and 8 mg PIP, which is within the range specified in the claims.

Applicant also notes the Experimental Examples presented in related U.S. Patent Application Nos. 10/984,683 [US 2005/0203130] and 10/580,962 [US 2007/0078162]. The Examples show the advantages of using pipamperone with citalopram to treat depression (Example 3), obsessive-compulsive disorder (Example 4), and panic disorder (Example 5). Obsessive-compulsive disorder and panic disorder are types of anxiety disorders (see, for example, "Diagnostic and Statistical Manual of Mental Disorders" published by the American Psychiatric Association, which is referred to in the first full paragraph on page 11 of the present application).

PK/PD modeling of pipamperone

In order to establish the *in vivo* receptor occupancy of pipamperone, the inventor conducted PK-PD modeling. By linking the pharmacokinetics and pharmaco-dynamics, a dose-concentration-response relationship was established and evaluated. Subsequently, the effect-time courses resulting from a drug dose were described and predicted. Efficacy of pipamperone, *i.e.* a 5-HT_{2A} receptor antagonistic effect, is expected with a Receptor Occupancy (RO) of ≥60% of 5-HT_{2A} at $C_{average}$ (C_{avg}), while adverse effects are expected with >10% Receptor Occupancy of D2 and H1 receptors at C_{avg}. The modeling indicates:

1. serotonin **5-HT_{2A}** receptor: a positive clinical effect, since over >60% RO;
2. dopamine-4 (**D4**) receptor: a positive clinical effect, since over >40% RO;
3. dopamine-2 (**D2**) receptor: absence of a negative effect, since <10% RO; and
4. histamine **H1** receptor: absence of a negative effect, since <10% RO.

Notably, relevant H1-receptor binding (>10% RO) results in sedative effects, while relevant D2-receptor binding (>10% RO) results in a neuroleptic effect and extrapyramidal symptoms (see e.g. Leysen et al. (1998), of record). This neuroleptic

sedative effect is not present at the claimed low dose of 5-15 mg pipamperone per day. On the other hand, relevant blockade of the **5-HT$_{2A}$** receptor and the **D4** receptor remains at the claimed low dose of 5-15 mg pipamperone per day. D4 receptor activation results in cognitive and behavioral problems, while 5-HT$_{2A}$ receptor activation results in negative feedback loop on 5-HT$_{1A}$ receptor activation. Thus, the negative effects which are experienced with other drugs are absent. These features are unique to a pipamperone, but only at a **low dose**. These features have never been recognized in the art, and even less their potential in combined medication.

From this study, the following conclusions can be made:

- The optimal dose range is 5 - 15 mg pipamperone per day; and
- The optimal dose is 10 mg pipamperone per day.

Hence the PK/PD modeling results substantiate the observations by the inventor in that low amounts of pipamperone have a relevant clinical effect. The modeling data are presented in the Buntinx et al. 2008 poster and the Buntinx et al. 2008 Abstract attached in the accompanying SIDS. A blow-up of the modeling plot from the poster is attached with the poster. See also Peremans et al. (2008) for data showing that low dose pipamperone blocks serotonin-2A receptors *in vivo* (submitted in accompanying SIDS).

The attached Wade et al. 2009 online abstract submission reports that a very low daily dose of pipamperone (5 mg) added to citalopram (40 mg) provided superior antidepressant effects and less discontinuations compared with citalopram alone (submitted in accompanying SIDS). In contrast, treatments with atypical antipsychotics are known to be associated with increased risk of discontinuation due to adverse events (see, e.g. meta-analysis by Nelson et al. 2009 in accompanying SIDS).

Wirz-Justice

The Examiner asserts that Wirz-Justice teaches a combination of pipamperone (20-

30 mg) and citalopram (10 mg) (Table 1, page 214). Rather, applicant respectfully notes that Wirz-Justice teaches administering citalopram (10 mg/d) to a subject already receiving the combination of risperidone (2-3 mg/d) and pipamperone (20-30 mg/d) (Table 1, page 214 left column). Wirz-Justice evaluated different drug combinations on the rest-activity cycle in Alzheimer disease. Wirz-Justice teaches that the effect of citalopram as an addition to the risperidone/pipamperone combination leads to a rest-activity cycle alteration, more specifically a peak of morning activity, less afternoon activity, and less movement during the first part of the night, in combination with a shift of the cycle to earlier. In conclusion, Wirz-Justice teaches the use of citalopram with a combination of risperidone and pipamperone**,** pipamperone at a high dose (20-30 mg/d), and the use of this combination to harmonize the rest-activity cycle in Alzheimer Disease. Wirz-Justice is silent about mood or anxiety disorders.

Medicaments Psychotropes

The Examiner asserts that Medicaments Psychotropes teaches an initial daily dose of 10 mg of pipamperone to be administered. Applicant respectfully notes that Medicaments Psychotropes teaches the dose of Dipiperon for children over the age of 5. A daily dose of 50 mg is recommended for the youngest child, i.e., a child of age 5 (5 drops per year of age ("5 gouttes x année d' âge") where 5 drops = 10 mg. This dose is accomplished by starting off with 10 mg (5 drops) on day one and increasing the dose with 10 mg (5 drops) per day until the final needed treatment dose is reached. Thus, it is recommended in Medicaments Psychotropes that children only <u>start</u> with a dose of 10 mg per day. This dose is subsequently increased by 10 mg per day to the daily dose that is recommended for the age of the child (e.g. 50 mg per day for a child of age 5 years, with higher doses for older children). In other words, the treatment dose is <u>not</u> the start dose.

Medicaments Psychotropes does *not* provide any information whatsoever on disorders or diseases that can be treated, even less on treating mood or anxiety disorders.

Dudley

Dudley relates to subject failing to respond to conventional antidepressants: Applicant notes that Dudley aims at and relates to treating a depressive disorder by administering compositions and combinations comprising a steroid in the testosterone synthetic pathway in subjects *failing to respond to conventional antidepressants* and/or who exhibited low or borderline testosterone levels (see paragraph 29). This is illustrated in Example 12, using a testosterone transdermal gel, where it is noted that the subjects were "taking adequate dose of antidepressant medication … but still complaining of depressive symptoms…" (paragraph 0508).

Dudley teaches an alternative: Dudley provides an alternative for subjects failing to respond to conventional antidepressants, in particular the use of testosterone. The use of testosterone pervades throughout the detailed description. The use of testosterone as the primary compound is explicitly confirmed in paragraphs 119 - 121, 148 - 162, the Examples in general, Examples 1 - 9 (paragraphs 246 - 492) in particular, paragraphs 472-473 relating to mood assessment in response to testosterone alone, the Figures and, first and foremost, the claims. Dudley provides testosterone as an alternative therapy for treating depressive disorders.

Exceptionally, Dudley provides that a further compound may be administered in conjunction with testosterone. Hence, the first compound is always and invariantly testosterone or a steroid in the testosterone synthetic pathway even in a combination of compounds. Paragraph 122 relates to "methods, kits, combinations and compositions" which are used *in conjunction* with a pharmaceutical agent, such as an antidepressant. In paragraph 124 "the present invention employs testosterone *in conjunction* with a

pharmacologically-effective amount of ... an anti-depressant" (emphasis added). The term "methods, kits, combinations and compositions for treating ...." used in Dudley, always comprises testosterone and possibly a second compound. In paragraphs 131 - 133, the antidepressant agents which can be used *in conjunction* with testosterone are exemplified. Although it is mentioned in the last sentence that combinations can be used of the antidepressants, these combinations are to be used *in conjunction* with testosterone. Hence, when considering Dudley the person skilled in the art would be taught administering at least testosterone when treating depression.

Isolating the combination citalopram - pipamperone amounts to undue burden: There is no incentive in Dudley to combine citalopram with pipamperone. Furthermore, neither of these compounds is a preferred compound (paragraph 133). In paragraph 132, over 140 antidepressants are listed. Each and every combination would encompass about 10^{158} possibilities. Even if only a combination of only two compounds is contemplated (which is denied), about 10,000 possibilities are disclosed. It would amount to undue burden to test each and every combination in order to come to pipamperone and citalopram (in particular considering that the subjects failed to respond to conventional antidepressants). In addition, further to the teachings of Dudley, any combination should be tested with at least three compounds, *i.e.* including testosterone.

In conclusion, applicant respectfully maintains that a person of ordinary skill in the art would never combine the teachings of documents Wirz-Justice, Medicaments Psychotropes and Dudley to arrive at the subject-matter of the claims of the current application. In particular, the cited references do not provide any teaching or motivation to use the claimed treatment dose of 5-15 mg pipamperone with a SSRI for treatment of a mood disorder or an anxiety disorder. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

2. Claims 81-85 are rejected as being unpatentable over Wirz-Justice et al. (Alzheimer Disease and Associated Disorders 14(4): 212-215, 2000), Medicaments Psychotropics and Bymaster et al. (WO 98/11897).

Claims 81-85 have been cancelled rendering this rejection moot.

Status of Related Canadian Application

Patent family member Canadian Patent Application No. 2,461,248 has been allowed. A copy of the Notice of Allowance is enclose with the Supplemental Information Disclosure Statement accompanying this reply.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/752,423. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on October 2, 2007, May 13, 2008, February 19, 2009, and August 5, 2009.

2. U.S. Patent Application No. 10/803,793. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on May 3, 2007, October 19, 2007, September 2, 2008, February 20, 2009 and November 10, 2009. Claims 50, 55, 92 and 93 are allowed.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007, February 22, 2008, October 21, 2008, and July 21, 2009.

4. U.S. Patent Application No. 10/580,962. The claims have been subject to a restriction requirement issued on March 6, 2009. An Office Action on the merits of the

application issued on June 2, 2009.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached forms PTO/SB/08A-B. A copy of each non-US patent document is attached hereto.

CONCLUSIONS

In view of the amendments and remarks made hereinabove, reconsideration and withdrawal of the rejections set forth in the June 10, 2009 Office Action and passage of the pending claims to allowance are respectfully requested. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

The Patent Office is authorized to charge Deposit Account No. 01-1785 for following fees for a small entity: the $555.00 fee for a three month extension of time and the $405.00 fee for filing a Request for Continued Examination (RCE). No additional fee is deemed necessary in connection with the filing of this response. However, if any other fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

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